NDC 44178-0552-1

ARIDOL™(mannitol inhalation powder) Bronchial Challenge Test Kit

Full Prescribing Information and Test Kit Instructions

Please see accompanying Full Prescribing Information, Boxed Warning, and Important Safety Information on the reverse side.

Aridol is a bronchoconstrictor agent for diagnostic purposes and should only be administered by a trained healthcare professional.

3 44178 05521 0

aridol™
(mannitol inhalation powder)
Bronchial Challenge Test Kit

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARIDOL safely and effectively. See full prescribing information for ARIDOL.

ARIDOL™ (mannitol inhalation powder)
Bronchial Challenge Test Kit
Initial U.S. Approval: 1964

WARNING: RISK OF SEVERE BRONCHOSPASM
See full prescribing information for complete boxed warning.
Mannitol, the active ingredient in ARIDOL, acts as a bronchoconstrictor and may cause severe bronchospasm. Bronchial challenge testing with ARIDOL is for diagnostic purposes only. Only trained professionals under the supervision of a physician who are familiar with the management of acute bronchospasm should perform bronchial challenge testing with ARIDOL. Medications (such as short acting inhaled beta-agonist) and equipment to treat severe bronchospasm must be present in the testing area. Because of the potential for severe bronchoconstriction, bronchial challenge testing with ARIDOL should not be performed in any patient with clinically apparent asthma or very low baseline pulmonary function tests (e.g., FEV_1<1-1.5 liters or <70% of the predicted values) (5.1)

INDICATIONS AND USAGE

Mannitol, the active ingredient in ARIDOL, is a sugar alcohol indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma. (1)

Limitations of Use: ARIDOL is not a stand alone test or a screening test for asthma. Bronchial challenge testing with ARIDOL should be used only as part of a physician's overall assessment of asthma.

DOSAGE AND ADMINISTRATION

For Oral Inhalation Use Only

- One ARIDOL test kit contains dry powder mannitol capsules in graduated doses and a single patient use inhaler necessary to perform one bronchial challenge test. (2)
- The mannitol capsules supplied in the ARIDOL kit are to be used with the single patient use inhaler device (2). Discard the inhaler after use.
- Capsule contents are to be inhaled in increasing dosage until either a positive response (15% reduction in FEV_1 from baseline or a 10% incremental reduction in FEV_1 between consecutive doses) is achieved or all capsules are inhaled (maximum total dose 635mg) (2)
- Starting and maximum dose is the same for children (≥6 years old) and adults (2)

DOSAGE FORMS AND STRENGTHS

Inhalation powder. One test kit contains dry powder mannitol capsules in graduated doses of 0mg, 5mg, 10mg, 20mg, and 40mg and one single patient use dry powder inhaler device (2, 3)

CONTRAINDICATIONS

- Known hypersensitivity to mannitol or to the gelatin used to make the capsules (4)
- Conditions that may be compromised by induced bronchospasm or repeated spirometry maneuvers (4)

WARNINGS AND PRECAUTIONS

- Severe bronchospasm: ARIDOL may cause severe bronchospasm in susceptible patients. Administer by trained professionals under the supervision of a physician. Medications and equipment to treat severe bronchospasm must be present in the testing area. (5.1)
- Subjects with co-morbid conditions: Use with caution in patients with conditions that may increase sensitivity to the bronchoconstricting or other potential effects of ARIDOL such as: severe cough, ventilatory impairment, unstable angina, or active upper or lower respiratory tract infection that may worsen with use of a bronchial irritant. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (rate ≥1%) were headache, pharyngolaryngeal pain, throat irritation, nausea, cough, rhinorrhea, dyspnea, chest discomfort, wheezing, retching and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmaxis Inc. at 1-888-659-6396 or email at adverse.events@pharmaxis.com.au or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Revised October 2010

See 17 for PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SEVERE BRONCHOSPASM
Mannitol, the active ingredient in ARIDOL, acts as a bronchoconstrictor and may cause severe bronchospasm. Bronchial challenge testing with ARIDOL is for diagnostic purposes only. Bronchial challenge testing with ARIDOL should only be conducted by trained professionals under the supervision of a physician familiar with all aspects of the bronchial challenge test and the management of acute bronchospasm. Medications (such as short acting inhaled beta-agonist) and equipment to treat severe bronchospasm must be present in the testing area. If severe bronchospasm occurs it should be treated immediately by administration of a short acting inhaled beta-agonist. Because of the potential for severe bronchoconstriction, the bronchial challenge testing with ARIDOL should not be performed in any patient with clinically apparent asthma or very low baseline pulmonary function tests (e.g., FEV_1 <1-1.5 liters or <70% of the predicted values) [*see Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

Mannitol, the active ingredient in ARIDOL, is a sugar alcohol indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma.

Limitations of Use:

ARIDOL is not a stand alone test or a screening test for asthma. Bronchial challenge testing with ARIDOL should be used only as part of a physician's overall assessment of asthma.

2 DOSAGE AND ADMINISTRATION

Basic Dosing Information

ARIDOL is a test kit containing the required capsules of dry powder mannitol for oral inhalation in graduated doses with the supplied single patient use inhaler necessary to perform one bronchial challenge test. The inhaler should be discarded after use.

Do not swallow ARIDOL capsules.

The airway response to bronchial challenge testing with ARIDOL is measured using forced expiratory volume in one second (FEV_1).

Prior to bronchial challenge testing with ARIDOL, standard spirometry should be performed and the reproducibility of the resting FEV_1 established.

An overview of the testing procedure can be found below. See the ARIDOL bronchial challenge test instructions for complete instructions on the dosing and spirometry procedures.

a. A nose clip may be used if preferred. If so, apply nose clip to the subject and direct the subject to breathe through the mouth
b. Insert 0 mg capsule into inhalation device. Puncture capsule by depressing buttons on side of device slowly, and once only (a second puncture may fragment the capsules)
c. The patient should exhale completely, before inhaling from device in a controlled rapid deep inspiration
d. At the end of deep inspiration, start 60 second timer, subject should hold breath for 5 seconds and exhale through mouth before removal of nose clip
e. At the end of 60 seconds, measure the FEV_1 in duplicate (the measurement after inhaling the 0 mg capsule is the baseline FEV_1)
f. Repeat steps a-e following the mannitol capsule dose steps from Table 1 below until the patient has a positive response or 635 mg of mannitol has been administered (negative test)

Table 1: Mannitol dose steps for bronchial challenge testing with ARIDOL

Dose #	Dose mg	Cumulative Dose mg	Capsules per dose
1	0	0	1
2	5	5	1
3	10	15	1
4	20	35	1
5	40	75	1
6	80	155	2 x 40 mg
7	160	315	4 x 40 mg
8	160	475	4 x 40 mg
9	160	635	4 x 40 mg

A positive response is achieved when the patient experiences a 15% reduction in FEV_1 from (0 mg) baseline (or a 10% incremental reduction in FEV_1 between consecutive doses). The test result is expressed as a PD_{15}.

Patients with either a positive response to bronchial challenge testing with ARIDOL or significant respiratory symptoms should receive a standard dose of a short acting inhaled beta-agonist and monitored until fully recovered to within baseline.

3 DOSAGE FORMS AND STRENGTHS

ARIDOL is a bronchial challenge test kit. Each kit contains one, single patient use, dry powder inhaler device and 3 consecutively numbered foil blister packs containing a total of 19 capsules of mannitol for oral inhalation as described below:

Blister pack "1":

- Marked 1 – 1 x empty clear capsule
- Marked 2 – 1 x 5 mg white/clear capsule printed with 5 mg
- Marked 3 – 1 x 10 mg yellow/clear capsule printed with 10 mg
- Marked 4 – 1 x 20 mg pink/clear capsule printed with 20 mg

Blister pack "2":

- Marked 5 – 1 x 40 mg red/clear capsule printed with 40 mg
- Marked 6 – 2 x 40 mg red/clear capsules printed with 40 mg
- Marked 7 – 4 x 40 mg red/clear capsules printed with 40 mg

Blister pack "3":

- Marked 8 – 4 x 40 mg red/clear capsules printed with 40 mg
- Marked 9 – 4 x 40 mg red/clear capsules printed with 40 mg

4 CONTRAINDICATIONS

ARIDOL use is contraindicated in:

- Patients with known hypersensitivity to mannitol or to the gelatin used to make the capsules
- Patients with conditions that may be compromised by induced bronchospasm or repeated spirometry maneuvers. Some examples include: aortic or cerebral aneurysm, uncontrolled hypertension, recent myocardial infarction or cerebral vascular accident [*see Warnings and Precautions (5.2)*].

5 WARNINGS & PRECAUTIONS

5.1 Severe Bronchospasm

Mannitol, the active ingredient in ARIDOL, acts as a bronchoconstrictor and may cause severe bronchospasm in susceptible patients. The test should only be conducted by trained professionals under the supervision of a physician familiar with all aspects of the bronchial challenge test and the management of acute bronchospasm. Patients should not be left unattended during the bronchial challenge test. Medications and equipment to treat severe bronchospasm must be present in the testing area.

If a patient has a ≥10% reduction in FEV_1 (from pre-challenge FEV_1) on administration of the 0 mg capsule, the ARIDOL bronchial challenge test should be discontinued and the patient should be given a dose of a short acting inhaled beta-agonist and monitored accordingly.

Patients with either a positive response to bronchial challenge testing with ARIDOL or significant respiratory symptoms should receive a short acting inhaled beta-agonist. Subjects should be monitored until fully recovered to within baseline.

5.2 Subjects with Co-morbid Conditions

Bronchial challenge testing with ARIDOL should be performed with caution in patients with conditions that may increase sensitivity to the bronchoconstricting or other potential effects of ARIDOL such as severe cough, ventilatory impairment, spirometry-induced bronchoconstriction, hemoptysis of unknown origin, pneumothorax, recent abdominal or thoracic surgery, recent intraocular surgery, unstable angina, or active upper or lower respiratory tract infection.

6 ADVERSE REACTIONS

Mannitol, the active ingredient in ARIDOL, is a sugar alcohol that may cause severe bronchospasm in susceptible subjects [*see Warnings and Precautions (5.1)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population for the ARIDOL bronchial challenge test consisted of 1,082 subjects (577 females and 505 males) including patients with asthma, symptoms suggestive of asthma, and healthy individuals from 6 to 83 years of age who participated in the two clinical trials (Studies 1 and 2). The racial distribution of subjects was 84% Caucasian, 5% Asian, 4% Black, and 7% Other. Children and adolescents comprised 23% of the total study population with 118 children aged 6-11 years and 128 adolescents aged 12-17 years.

Adverse reactions were reported at the time of the testing procedure and for one day thereafter. No serious adverse reactions were reported following bronchial challenge testing with ARIDOL in either trial.

Five adult subjects (0.6%) discontinued from the studies within a day following bronchial challenge testing with ARIDOL because of cough, decreased lung function, feeling jittery, sore throat, and throat irritation. One adult subject (0.3%) discontinued following the methacholine bronchial challenge test because of dizziness. One pediatric subject (0.4%) discontinued from the studies within a day following bronchial challenge testing with ARIDOL because of retching.

Table 2 displays the combined common adverse reactions (≥1%) within a day after bronchial challenge testing with ARIDOL or methacholine in the overall population for Studies 1 and 2.

Table 2: Adverse reactions with an incidence ≥1% within a day after bronchial challenge testing (overall population, Studies 1 and 2 combined)

Adverse Reactions	TREATMENT	
	ARIDOL (N=1046) n (%)	Methacholine Challenge (N=420) n (%)
Headache	59 (6)	4 (1)
Pharyngolaryngeal pain	25 (2)	0
Throat irritation	19 (2)	1 (<1)
Nausea	19 (2)	0
Cough	17 (2)	8 (2)
Rhinorrhea	16 (2)	0
Dyspnea	15 (1)	21 (5)
Chest discomfort	13 (1)	18 (4)
Wheezing	8 (1)	6 (1)
Retching	6 (1)	0
Dizziness	5 (1)	13 (3)

The maximum reduction in FEV_1 following bronchial challenge testing with ARIDOL was 46%, compared to 54% for exercise testing and 67% for the methacholine challenge. The incidences in decreases in FEV_1 ≥30% and ≥60% following ARIDOL, methacholine, and exercise challenges for Studies 1 and 2 is shown in Table 3.

Table 3: Incidence of decreases in FEV_1 ≥30% or ≥60% (overall population, Studies 1 and 2)

Challenge	No. Exposed	N (%) with Fall in FEV_1 ≥30%	N (%) with Fall in FEV_1 ≥60%
Study 1			
Exercise	435	27 (6%)	0
Methacholine	420	51 (12%)	3 (1%)
ARIDOL	419	3 (1%)	0
Study 2			
ARIDOL asthmatics	536	23 (4%)	0
ARIDOL Non-asthmatics	91	0	0

There were no differences in the incidence of adverse reactions based on gender or race. The clinical trials did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently compared to subjects below 65 years of age.

Children and Adolescents Aged 6 to 17 Years: Overall, the types and severities of adverse reactions in children were similar to those observed in the adult population. As in the adult population, the adverse reactions of pharyngolaryngeal pain, nausea, and headache were the more common with incidences of 4%, 3%, and 3%, respectively. There were no major differences in the types of adverse reactions observed in children 6-11 years of age compared to adolescents 12-17 years old.

The decrease in FEV_1 in children and adolescents who received the ARIDOL bronchial challenge test was similar to that of the adult population with 5%, 15% and 9% of pediatric subjects who had bronchial challenge testing with ARIDOL, methacholine and exercise, respectively, experiencing reduction in FEV_1 ≥30%. No patient who had bronchial challenge testing with ARIDOL or exercise had a decrease in FEV_1 ≥60%, whereas, one adolescent patient (aged 12 years) who received methacholine had a decrease in FEV_1 ≥60%.

6.2 Post-Marketing Experience

The following adverse reactions have been identified post approval outside the U.S. of the ARIDOL bronchial challenge test kit: cough, gagging, wheeze, and decreased forced expiratory volume. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with mannitol, the active ingredient in ARIDOL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled clinical studies of mannitol in pregnant women. Bronchial challenge testing with ARIDOL should be performed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: Mannitol was not teratogenic. Mannitol did not cause any embryofetal malformations when given to pregnant rats and mice at oral doses approximately 20 and 10 times the maximum recommended human daily inhalation dose (MRHDID) in adults, respectively, on a mg/m^2 basis [*see Animal Toxicology and/or Pharmacology (13.2)*].

8.2 Labor and Delivery

The effects of a possible hyperresponsiveness reaction on a mother or child during labor or delivery are not known, and therefore bronchial challenge testing with ARIDOL should not be administered during labor or delivery.

8.3 Nursing Mothers

It is not known whether mannitol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mannitol is given to a nursing mother.

8.4 Pediatric Use

A total of 246 children and adolescents ages 6 to 17 years were studied in the two clinical trials [*see Clinical Studies (14)*].

The mean and median maximum percentage reduction in FEV_1 in patients with a positive ARIDOL challenge test in children and adolescents 6 to 17 years of age (19% and 18%, respectively) showed no apparent difference compared to the adult population (19% and 18%, respectively).

The safety profile of the ARIDOL bronchial challenge test in children and adolescents 6 to 17 years of age was similar to the adult population in two clinical studies [*see Adverse Reactions (6)*].

Bronchial challenge testing with ARIDOL should not be performed in children less than 6 years of age due to their inability to provide reliable spirometric measurements.

8.5 Geriatric Use

There was insufficient number of subjects 50 years of age and older in the clinical program. Therefore, the safety and efficacy of bronchial challenge testing with ARIDOL in the older population cannot be adequately assessed. It is unknown whether any differences in the safety and efficacy of bronchial challenge testing with ARIDOL exist between subjects 50 years of age and older and younger subjects.

8.6 Hepatic and Renal Impairment

Formal pharmacokinetic studies with mannitol, the active ingredient, in ARIDOL, have not been conducted in patients with hepatic or renal impairment. However, an increase in systemic exposure of mannitol can be expected in patients with renal impairment based on the kidney being its primary route of elimination.

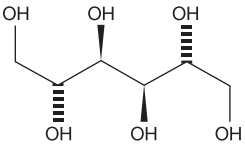
Given parenterally, mannitol is used as an osmotic diuretic in a variety of clinical situations including acute renal failure where the osmotic effects of mannitol inhibit the rate of water re-absorption and maintain the rate of urine production.

10 OVERDOSAGE

Mannitol, the active ingredient in ARIDOL, is to be administered only by inhalation. Susceptible persons may experience excessive bronchospasm from an overdose. If such bronchospasm occurs, immediately administer a short acting inhaled beta-agonist and other medical treatments such as oxygen, as necessary.

11 DESCRIPTION

D-mannitol (referred to throughout as mannitol), the active ingredient in ARIDOL is a hexahydric alcohol, that is a sugar alcohol, with the following chemical name (2R,3R,4R,5R)-hexane-1,2,3,4,5,6-hexol and chemical structure:



Mannitol is a white or almost white crystalline powder of free-flowing granules with an empirical formula of $C_6H_{14}O_6$ and molecular weight of 182.2. Mannitol is freely soluble in water, and very slightly soluble in alcohol. Mannitol shows polymorphism.

The ARIDOL bronchial challenge test kit contains one single patient use dry powder inhaler and 3 consecutively numbered foil blister packs containing a total of 19 capsules of mannitol for oral inhalation. All except the 0 mg printed hard gelatin capsules contain dry powder mannitol for oral inhalation. The accompanying dry powder inhaler is a plastic device used for inhaling the capsules. All doses are to be administered using the same device supplied with each kit without washing or sterilizing the device at anytime during the test.

To use the delivery system, a mannitol capsule is placed in the well of the inhaler, and the capsule is pierced by pressing and releasing the buttons on the side of the device. The mannitol dry powder is dispersed into the air stream when the patient inhales rapidly and deeply through the mouthpiece.

There are no inactive ingredients in the mannitol capsules supplied with the ARIDOL bronchial challenge test kit. The 0 mg capsule and the bodies of the 5, 10, 20 and 40 mg capsules are clear. The white caps (5 mg) contain titanium dioxide. The yellow caps (10 mg) contain titanium dioxide and yellow iron oxide. The pink caps (20 mg) and red caps (40 mg) contain titanium dioxide and red iron dioxide. The inhaler is a plastic device used for administering mannitol to the lungs. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Under standardized in vitro testing at a fixed flow rate of 60 L/min for 2 seconds, the delivered dose from the inhaler from each of the 5, 10, 20 and 40 mg capsules is approximately 3.4, 7.7, 16.5 and 34.1 mg, respectively. Peak inspiratory flow rates (PIFR) achievable through the inhaler were evaluated in healthy and asthmatic individuals ranging from 7 to 65 years of age and with % FEV_1 of predicted ranging from 67% to 123%. PIFR achieved in the study was at least 70.8 L/min in all subjects assessed. The mean PIFR was 118.2 L/min and approximately ninety percent of each population studied generated a PIFR through the device exceeding 90 L/min.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms through which inhaled mannitol causes bronchoconstriction are not known.

12.2 Pharmacodynamics

The response to inhaled mannitol is reported as the delivered dose of mannitol causing a 15% reduction in FEV_1 and is expressed as PD_{15}.

12.3 Pharmacokinetics

Absorption: The rate and extent of absorption of mannitol after oral inhalation was generally similar to that observed after oral administration. In a study of 18 healthy adult male subjects the absolute bioavailability of mannitol powder following oral inhalation was 59% while the relative bioavailability of inhaled mannitol in comparison to orally administered mannitol was 96%. Following oral inhalation of 635 mg, the mean mannitol peak plasma concentration (C_{max}) was 13.71 mcg/mL while the mean extent of systemic exposure (AUC) was 73.15 mcg•hr/mL. The mean time to peak plasma concentration (T_{max}) after oral inhalation was 1.5 hour.

Distribution: Based on intravenous administration, the volume of distribution of mannitol was 34.3 L.

Metabolism: The extent of metabolism of mannitol appears to be small. This is evident from a urinary excretion of about 87% of unchanged drug after an intravenous dose to healthy subjects.

Elimination: Following oral inhalation, the elimination half-life of mannitol was 4.7 hours. The mean terminal elimination half-life for mannitol in plasma remained unchanged regardless of the route of administration (oral, inhalation, and intravenous). The urinary excretion rate versus time profile for mannitol was consistent for all routes of administration. The total clearance after intravenous administration was 5.1 L/hr while the renal clearance was 4.4 L/hr. Therefore, the clearance of mannitol was predominately via the kidney. Following inhalation of 635 mg of mannitol in 18 healthy subjects, about 55% of the total dose was excreted in the urine as unchanged mannitol. Following oral or intravenous administration of a 500 mg dose, the corresponding values were 54% and 87% of the dose, respectively.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using ARIDOL have not been conducted in patients with hepatic or renal impairment. Since the drug is eliminated primarily via the kidney, an increase in systemic exposure can be expected in renally impaired patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year carcinogenicity studies in rats and mice mannitol did not show evidence of carcinogenicity at oral dietary concentrations up to 5% (or 7,500 mg/kg on a mg/kg basis). These doses were approximately 55 and 30 times the MRHDID, respectively, on a mg/m^2 basis.

Mannitol tested negative in the following assays: bacterial gene mutation assay, in vitro mouse lymphoma assay, in vitro chromosomal aberration assay in WI-38 human cells, in vivo chromosomal aberration assay in rat bone marrow, in vivo dominant lethal assay in rats, and in vivo mouse micronucleus assay.

The effect of inhaled mannitol on fertility has not been investigated.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies
Mannitol did not cause any embryofetal malformations when given to pregnant rats and mice at oral doses of 1.6 g/kg each (approximately 20 and 10 times the MRHDID in adults, respectively, on a mg/m^2 basis).

14 CLINICAL STUDIES

The effectiveness of the ARIDOL bronchial challenge test kit in assessing bronchial hyperresponsiveness in adults and children 6 years of age and older was assessed in two clinical studies. Study 1 was an operator-blinded, open-label crossover trial that assessed the sensitivity and specificity of bronchial challenge testing with ARIDOL compared with a methacholine bronchial challenge test in detecting bronchial hyperresponsiveness in subjects with symptoms suggestive of asthma but without a definite diagnosis of asthma. During the course of the study subjects underwent three types of bronchial challenge tests utilizing exercise, ARIDOL, and methacholine. A positive exercise test was defined as a decrease in FEV_1 ≥10%, a positive bronchial challenge test with ARIDOL was defined by either a decrease in FEV_1 by ≥15% from baseline or a between-dose reduction in FEV_1 ≥10%, and a positive methacholine response was defined as a decrease in FEV_1 ≥20% after breathing methacholine at a concentration less than or equal to 16 mg/mL. The sensitivity and specificity of bronchial challenge testing with ARIDOL and methacholine were then assessed relative to exercise testing which served as a common comparator. The sensitivity and specificity of ARIDOL and methacholine challenges were also assessed using a blinded study physician's diagnosis of asthma at the end of the study. Five-hundred nine subjects aged 6 to 50 years were screened for enrolment with 419 and 420 subjects receiving at least one dose of mannitol, the active ingredient in ARIDOL, or methacholine, respectively. The maximum cumulative dose of mannitol was 635 mg. Bronchial challenge testing with ARIDOL and methacholine demonstrated similar sensitivity and specificity in predicting bronchial hyperresponsiveness defined by a positive exercise challenge (Table 4).

Table 4: Comparisons of the sensitivity and specificity (calculated relative to exercise challenge) for the ARIDOL test and methacholine in Study 1

Population	Treatment	Sensitivity % (95% CI)	Specificity % (95% CI)
Overall Population (n=419)			
	ARIDOL	58 (50, 65)	63 (57, 69)
	Methacholine	53 (46, 51)	68 (62, 73)
	Difference	5 (-4, 13)	-5 (-12, 3)
Age 6-11 years old (n=36)			
	ARIDOL	67 (47, 87)	47 (21, 72)
	Methacholine	71 (52, 91)	33 (9, 57)
	Difference	-5 (-29, 20)	17 (-29, 62)
Age 12-17 years old (n=70)			
	ARIDOL	55 (37, 72)	62 (46, 77)
	Methacholine	65 (48, 81)	64 (49, 79)
	Difference	-10 (32, 13)	-3 (-24, 19)

Bronchial challenge testing with ARIDOL and methacholine also demonstrated similar sensitivity and specificity when calculated relative to a blinded study physician's diagnosis of asthma in subjects at the end of the study.

The sensitivity and specificity of bronchial challenge testing with ARIDOL in children and adolescents 6 to 17 years of age in Study 1 was similar to that in the overall population (Table 4).

Study 2 was a crossover study comparing bronchial challenge testing with ARIDOL to hypertonic (4.5%) saline in identifying bronchial hyperresponsiveness in subjects 6 to 83 years of age with (n=551) and without (n=95) asthma. In this study the efficacy endpoint of interest was an estimation of the sensitivity and specificity of bronchial challenge testing with ARIDOL with respect to a physician's clinical diagnosis of asthma. Following completion of the bronchial challenge tests with ARIDOL and hypertonic saline, a respiratory physician assessed the data and categorized the subjects as having or not having asthma. The sensitivity of the ARIDOL bronchial challenge test in subjects with a physician diagnosis of asthma was 58% [(54%, 62%, 95th CI)] compared to a sensitivity of the physician diagnosis in the same population of 97% [(95%, 98%, 95th CI)]. The specificity of the ARIDOL bronchial challenge test in subjects without asthma was 95% [(90%, 99%, 95th CI)] compared to the specificity of the physician diagnosis of 98% [(95%, 100%, 95th CI)].

16 HOW SUPPLIED/STORAGE AND HANDLING

ARIDOL is a bronchial challenge test kit. Each kit contains one single patient use, dry powder inhaler device and 3 consecutively numbered foil blister packs containing a total of 19 capsules of mannitol for oral inhalation as described below:

Blister pack "1":

- Marked 1 – 1 x empty clear capsule
- Marked 2 – 1 x 5 mg white/clear capsule printed with 5 mg
- Marked 3 – 1 x 10 mg yellow/clear capsule printed with 10 mg
- Marked 4 – 1 x 20 mg pink/clear capsule printed with 20 mg

Blister pack "2":

- Marked 5 – 1 x 40 mg red/clear capsule printed with 40 mg
- Marked 6 – 2 x 40 mg red/clear capsules printed with 40 mg
- Marked 7 – 4 x 40 mg red/clear capsules printed with 40 mg

Blister pack "3":

- Marked 8 – 4 x 40 mg red/clear capsules printed with 40 mg
- Marked 9 – 4 x 40 mg red/clear capsules printed with 40 mg

NDC-44178-0552-1

ARIDOL should be stored below 77°F (25°C) with excursions permitted between 59-86°F (15-30°C). [See USP Controlled Room Temperature]. Do not freeze. Do not refrigerate.

The ARIDOL bronchial challenge test should only be used with the provided inhaler. All remaining unused (opened and unopened) blister packs and the inhaler should be properly discarded at the completion of the test. Be sure to read the accompanying ARIDOL bronchial challenge test kit instructions completely before test initiation. If you have any questions, contact the manufacturer support at 1-888-659-6396.

17 PATIENT COUNSELING INFORMATION

17.1 Severe Bronchospasm

Prior to administration patients should be informed of the potential for bronchial challenge testing with ARIDOL to cause severe bronchospasm and of the potential symptoms they may experience.

17.2 Subjects with Certain Co-morbid Conditions

Bronchial challenge testing with ARIDOL should be performed with caution in patients having severe cough, ventilatory impairment, spirometry-induced bronchoconstriction, hemoptysis of unknown origin, pneumothorax, recent abdominal or thoracic surgery, recent intraocular surgery, unstable angina, or active upper or lower respiratory tract infection or other conditions that may worsen with the use of a bronchial irritant.

Manufactured by:
Pharmaxis Ltd
Unit 2, 10 Rodborough Rd
Frenchs Forest NSW 2086
AUSTRALIA

Manufactured for:
Pharmaxis, Inc.
One East Uwchlan Avenue, Suite 405
Exton, PA 19341
1-888-659-6396
www.aridol.info

SP-200-01

CPS480/01

This test instruction sheet has been approved by the U.S. Food and Drug Administration.

PLEASE REFER TO THE FULL PRESCRIBING INFORMATION BEFORE PERFORMING THIS ARIDOL BRONCHIAL CHALLENGE TEST.

Further information can be found at: www.ARIDOL.info or call Pharmaxis customer support (toll free) at:

1-888-659-6396

Manufactured by:
Pharmaxis Ltd.
Unit 2, 10 Rodborough Rd
Frenchs Forest NSW 2086 AUSTRALIA

Manufactured for:
Pharmaxis, Inc.
One East Uwchlan Ave, Suite 405
Exton, PA 19341
Part Number (SP-478-01, Rev October 2010)

aridol™

(mannitol inhalation powder)
Bronchial Challenge Test Kit

Important Test Information

a. The inhaler is for SINGLE PATIENT USE ONLY (one inhaler per ARIDOL bronchial challenge test) and should not be cleaned during the ARIDOL bronchial challenge test. Discard following each ARIDOL bronchial challenge test. Do not sterilize and reuse.

b. When patients are exhaling during the ARIDOL bronchial challenge test, ensure they do so AWAY from the inhaler to minimize humidity within the inhaler.

c. Pierce the capsule only once by fully depressing both piercing buttons on the sides of the inhaler simultaneously. (A second puncture may cause the capsule to split/fragment.)

d. Using rubber/latex gloves when administering the test and handling mannitol capsules may increase static and inhibit capsule movement within the inhaler.

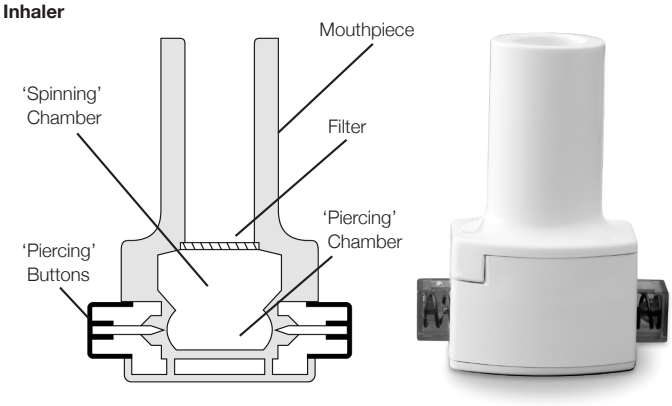
e. If static is an issue or the sound of the capsule 'rattling' cannot be heard during inhalation of mannitol, firmly tap the base of the inhaler with one hand while holding the inhaler with the other hand (mouthpiece facing downwards at a 45° angle). This should ensure that the capsule has been 'dislodged' and moved from the piercing chamber into the spinning chamber.

f. Inhalation of mannitol may cause a cough and/or dry throat. This is normal and expected when conducting an ARIDOL bronchial challenge test. You can offer the patient water to sip during and after the ARIDOL bronchial challenge test.

g. The ARIDOL bronchial challenge test is time critical and requires an osmotic gradient to be established and maintained. Prolonged intervals between doses may affect the validity of test results and should be avoided.

ARIDOL™ (mannitol inhalation powder) Bronchial Challenge Test Kit Instructions

Inhaler



ARIDOL Bronchial Challenge Test Results

Positive ARIDOL Bronchial Challenge Test Result
A positive response may be achieved in two ways:
≥ 15% fall in FEV_1 from baseline (using the post 0mg FEV_1 as baseline)
≥ 10% incremental fall in FEV_1 (between two consecutive mannitol doses)

Negative ARIDOL Bronchial Challenge Test Result
An ARIDOL bronchial challenge test result is considered to be negative when a cumulative dose of 635mg of mannitol has been administered and the patient's FEV_1 has not fallen by ≥ 15% from baseline.

Equipment Required:

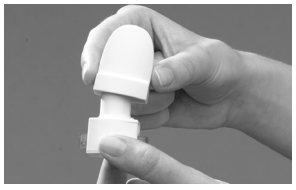
ARIDOL Bronchial Challenge Test Kit
(containing mannitol capsules, an inhaler, full prescribing information and instructions)
Spirometer & mouthpiece
Nose clip
Timer (which can be set to 60 seconds)
Calculator
Short-acting inhaled beta agonist (i.e. albuterol) and volumetric spacer (if using a metered dose inhaler)

Medication and emergency equipment should be present in the testing area in accordance with standard bronchial challenge test procedures.

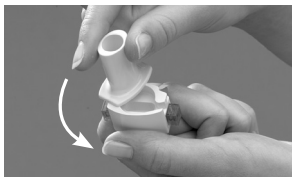
Inhaler Instructions

These instructions show you how to use the inhaler supplied in the ARIDOL™ (mannitol inhalation powder) Bronchial Challenge Test Kit.

1. **Remove Cap:** Using both hands, hold the inhaler upright and remove the cap.



2. **Open:** Hold the base of the inhaler firmly with one hand and open the inhaler by rotating the mouthpiece in the direction of the arrow as shown.

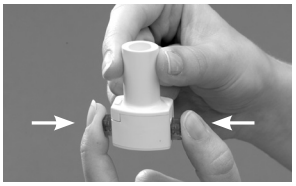


3. **Load:** Using dry hands, remove a capsule from the mannitol foil and place into the inhaler as shown. It does not matter which way the capsule is placed in the chamber.

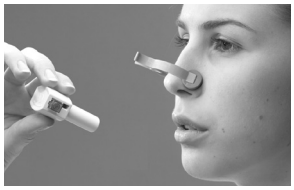
4. **Close:** Keeping the inhaler in an upright position, twist the mouthpiece into the closed position until you hear it 'click'.

5. **Pierce Capsule:** Hold the inhaler in an upright position and fully depress both piercing buttons on the sides of the inhaler simultaneously and only once (a second puncture may cause the capsule to split/fragment).

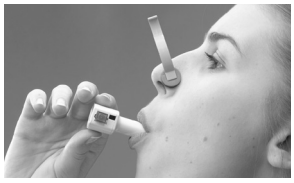
   The piercing action makes holes in the capsule and allows the powder inside the capsule to be released when the patient inhales through the mouthpiece of the inhaler.



6. **Prepare for Inhalation:** Tilt the inhaler so that the mouthpiece faces slightly downward at a 45° angle as shown. This allows the capsule to drop forward into the spinning chamber. A nose clip may be used, if preferred. If so, apply the nose clip to the subject and direct the subject to breathe through his/her mouth. Keep the inhaler tilted in this way and instruct the patient to exhale completely (away from the inhaler).

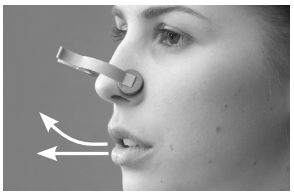


7. **Inhale:** The patient should tilt his/her head back slightly, keep the inhaler at a 45° angle, raise the inhaler to his/her mouth and ensure they close their lips tightly around the mouthpiece. The patient should take a controlled and deep inhalation. The patient should then hold their breath for five seconds.

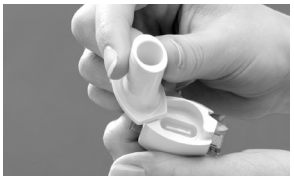


Note: During a successful inhalation you should hear a 'rattling' sound as the capsule empties and spins in the inhaler.

8. **Exhale:** Remove the inhaler from the patient's mouth, allow him/her to exhale and resume normal breathing.



9. **Check:** The mannitol capsule must spin in the inhaler in order to empty. A second inhalation (using the same capsule) may be required immediately if the capsule is not emptied sufficiently following the first inhalation. Check the capsule following each inhalation.



Please Note:
The inhaler is designed for SINGLE PATIENT USE ONLY (one inhaler per ARIDOL bronchial challenge test) and should not be cleaned during the ARIDOL bronchial challenge test. Discard the inhaler following each ARIDOL bronchial challenge test. Do not reuse.

ARIDOL™ (mannitol inhalation powder) Bronchial Challenge Test Kit Procedure

STEP 1: Patient should be seated for the test. Explain the test procedure; include what is required for an FVC maneuver and FEV_1 measurement and the type of inhalation flow required for the inhaler. Demonstrate as required.

STEP 2: Enter the patient's information in the spirometer as applicable (age, height, race, date of birth, gender, etc.).

STEP 3: Determine the pre-challenge FEV_1
Ask the patient to perform an FVC maneuver according to the **ATS/ERS Guidelines.** The patient's FEV_1 should be ≥ 70% predicted. The ARIDOL bronchial challenge test should not be performed in patients with an FEV_1 of less than 70% predicted.

STEP 4: Calculate the baseline FEV_1 (0mg)

a. Remove the **0mg** mannitol capsule from the foil, twist open the inhaler (as per the arrow on the inhaler), place the capsule inside and close the inhaler.

b. Pierce the capsule only once by fully depressing both piercing buttons on the sides of the inhaler simultaneously.

c. A nose clip may be used, if preferred. If so, apply the nose clip to the subject and direct the subject to breathe through his/her mouth.

d. Tilt the inhaler at a 45º angle (mouthpiece down). Check that the capsule has moved from the piercing chamber into the spinning chamber closest to the mouthpiece. You can often hear the capsule fall forward or see the capsule through the vents on each side of the inhaler. Give the inhaler to the patient ensuring that they keep the inhaler at the same 45º angle.

e. Ensure the patient is sitting up straight. Ask the patient to exhale (away from the inhaler), seal his/her lips around the inhaler mouthpiece and take a controlled and deep inhalation. During a successful inhalation, a 'rattling' sound should be heard as the capsule spins within the inhaler.

f. Ask the patient to hold their breath for five seconds after inhalation. At the end of the patient's inhalation, start a 60 second timer. When five seconds has passed, instruct the patient to exhale through their mouth (away from the inhaler), remove the nose clip and breathe normally.

g. When the timer beeps after 60 seconds, immediately instruct the patient to perform two acceptable FEV_1 measurements. **Record the highest FEV_1 reading as the baseline FEV_1.** *If the highest FEV_1 is ≥ 10% drop from the pre-challenge FEV_1, do not continue with the test.*

h. **Calculate the target FEV_1:** A positive ARIDOL bronchial challenge test result is achieved when the patient's FEV_1 falls ≥15% from their baseline FEV_1. To calculate the target FEV_1, multiply the baseline FEV_1 (the highest reading obtained at 0mg) obtained in Step 4.g by 0.85. Record this value.

STEP 5: 5mg capsule

a. Insert the 5mg capsule into the inhaler and pierce the capsule as in Step 4.a & 4.b.

b. Repeat Steps 4.c – 4.f.

c. Following inhalation remove the capsule from the inhaler and check to ensure it has been emptied sufficiently; if not, a second inhalation will be required immediately.

d. Load the 10mg capsule to prepare for the next dose.

e. At 60 seconds following inhalation, immediately measure the patient's FEV_1 two times (acceptability criteria must be met). Use the highest of these two values to calculate the change in FEV_1.

f. Compare the FEV_1 value at this dose to the target FEV_1. If the FEV_1 value is equal to or below the target value, or there has been an incremental fall of ≥ 10% from the previous dose, the ARIDOL bronchial challenge test is positive and complete. If not, immediately proceed to the next dose (Step 6).

STEP 6: 10mg, 20mg, 40mg Capsules
Administer the 10mg, 20mg and 40mg doses following the directions given (in Step 5) for the 5mg dose. Each dose is one capsule.

STEP 7: 80mg dose (2 x 40mg capsules)

a. Insert and pierce the first of the two 40mg capsules that comprise the 80mg dose.

b. The patient should inhale the dose in the same manner as previous doses, hold their breath for five seconds then exhale.

c. Remove the first 40mg capsule from the inhaler and check to ensure it has been emptied sufficiently; if not, a second inhalation will be required immediately. Do this following the administration of each capsule.

d. Following inhalation, load the second 40mg capsule and give to the patient immediately following exhalation after the first 40mg capsule.

e. Instruct the patient to inhale the second capsule immediately to **ensure that the osmotic effect of mannitol is cumulative.**

f. Set the timer for 60 seconds when the second 40mg capsule has been inhaled.

g. Instruct the patient to hold their breath for five seconds before exhaling.

h. At 60 seconds following inhalation of the second capsule, immediately measure the patient's FEV_1 two times *(according to **ATS/ERS Guidelines**)*. Use the higher of these two values to calculate the change in FEV_1.

i. Compare the FEV_1 value at this dose to the target FEV_1. If the FEV_1 value is equal to or below the target value, or there has been an incremental fall of ≥ 10% from the previous dose, the ARIDOL bronchial challenge test is positive and complete. If not, immediately proceed to the next dose (Step 8).

STEP 8: First 160mg dose (4 x 40mg capsules)

a. Insert and pierce the first of the four 40mg capsules that comprise the 160mg dose.

b. The patient should inhale the dose in the same manner as previous doses, hold their breath for five seconds then exhale.

c. Remove capsule from the inhaler and check to ensure it has been emptied sufficiently; if not, a second inhalation will be required immediately. Do this following the administration of each capsule.

d. Following inhalation, load the second 40mg capsule and give to the patient immediately following exhalation.

e. The patient should inhale the contents of the second capsule, hold their breath for five seconds then exhale.

f. Following inhalation, load the third 40mg capsule and give to the patient immediately following exhalation.

g. The patient should inhale the contents of the third capsule, hold their breath for five seconds then exhale.

h. Immediately following inhalation, load the fourth 40 mg capsule and give to the patient immediately following exhalation.

i. Instruct the patient to inhale the fourth capsule immediately to **ensure that the osmotic effect of mannitol is cumulative.**

j. Set the timer for 60 seconds when the fourth 40mg capsule has been inhaled.

k. Instruct the patient to hold their breath for five seconds before exhaling.

l. At 60 seconds following inhalation of the fourth capsule, immediately measure the patient's FEV_1 two times *(according to **ATS/ERS Guidelines**)*. Use the higher of these two values to calculate the change in FEV_1.

m. Compare the FEV_1 value at this dose to the target FEV_1. If the FEV_1 value is equal to or below the target value, or there has been an incremental fall of ≥ 10% from the previous dose, the ARIDOL bronchial challenge test is positive and complete. If not, immediately proceed to the next dose (Step 9).

STEP 9: Second 160mg dose (4 x 40mg capsules)
Administer the second 160mg dose following the directions given in Step 8.

STEP 10: Third 160mg dose (4 x 40mg capsules)
Administer the third 160mg dose following the directions given in Step 8.

At the completion of this dose, 635mg has been administered. If a positive response has not been met, the ARIDOL bronchial challenge test should be considered negative and complete.

STEP 11: Following completion of the ARIDOL bronchial challenge test with a positive result or significant respiratory symptoms (e.g. wheezing, dyspnea, cough), you should administer a short-acting inhaled beta agonist and monitor the patient until fully recovered to within baseline. In the case of a negative result, if the patient has significant respiratory symptoms, a short-acting inhaled beta agonist should be administered.

NDC 44178-0552-1

Aridol™(mannitol inhalation powder) **Bronchial Challenge Test Kit**

pharmaxis

Manufactured by:
Pharmaxis Ltd
Unit 2, 10 Rodborough Rd
Frenchs Forest NSW 2086
AUSTRALIA

Manufactured for:
Pharmaxis, Inc.
One East Uwchlan Avenue, Suite 405
Exton, PA 19341

phone: 888-416-1828
www.aridol.info
www.pharmaxis.com.au

US-A-12-10-066 Printed in U.S.A./December 2010